DNA methylation may associated with atrial remodeling in pressure-overload murine model.

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Introduction: Atrial fibrillation (AF) is one of the most common arrhythmias in Japan. Atrial remodeling, characterized by the electrical and structural changes in the atrium, is the critical mechanism for the initiation and progression of AF. Several reports suggested that the restoration of sinus rhythm by catheter ablation attenuated the atrial remodeling in time dependent manner, which was called reverse remodeling. On the other hand, it is also well known that the atrial remodeling remains in patients with long-lasting persistent AF even after the restoration of sinus rhythm. These findings suggested that some irreversible process might play a role in the progression of atrial remodeling. Although the precise mechanism of reverse remodeling has not been fully elucidated, several reports have suggested that the epigenetic change is associated with the development of AF. We hypothesized that the methylation of DNA, one of the epigenetic regulations was involved in the progression of atrial remodeling.

Methods: Male mice (C57BL/6J) underwent transverse aortic constriction (TAC) procedure to generate a pressure-overload model of atrial remodeling. Sham-operative mice were utilized for the control. After the extraction of genomic DNA from the left atrium, the comprehensive analysis of the DNA methylation was performed with methyl-CpG-binding domain (MBD)-sequence. In another set of mice, RNA was extracted from the left atrium, followed by the RNA-sequence. These 2 comprehensive analyses using next-generation sequencer were analyzed in combination. After the identification of genes with the change in DNA methylation and RNA expression, the expression change of mRNA was confirmed in another set of TAC-operated mice and controls (n=5 each).

Result: We found that 17 genes had reduced expression of RNA with concentrated MBD-seq, indicating the increased DNA methylation suppressed the expression of RNA. We also found 4 genes showed increased expression of RNA with diluted MBD-seq, suggesting the reduced DNA methylation enhanced the expression of RNA.

Conclusion: Change in the status of DNA methylation may be linked with the expression of RNA in pressure-overload murine atria. These findings have possibility to explain the irreversible process of atrial remodeling.